VENOUS THROMBOEMBOLISM (VTE)

Venous thromboembolism (VTE) is a condition in which a blood clot forms most often in the deep veins of the leg, groin or arm (known as deep vein thrombosis, DVT) and travels in the circulation, lodging in the lungs (known as pulmonary embolism, PE). Together, DVT and PE are known as VTE - a dangerous, potentially deadly medical condition.

Types of Thrombosis:

- **Deep vein thrombosis (DVT)**: A blood clot that forms in a deep vein, usually the leg, groin or arm.
- **Pulmonary embolism (PE)**: A blood clot that occurs when a DVT clot breaks free from a vein wall and travels to the lungs blocking some or all of the blood supply. PE can often be fatal.
- **DVT + PE = VTE**: DVT and PE are collectively referred to as VTE.

Etiology:

The most common triggers for venous thromboembolism are surgery, cancer, immobilization and hospitalization.

Deep vein thrombosis forms in the legs when something slows or changes the flow of blood. In women, pregnancy and the use of hormones like oral contraceptives or estrogen for menopause symptoms can also play a role.

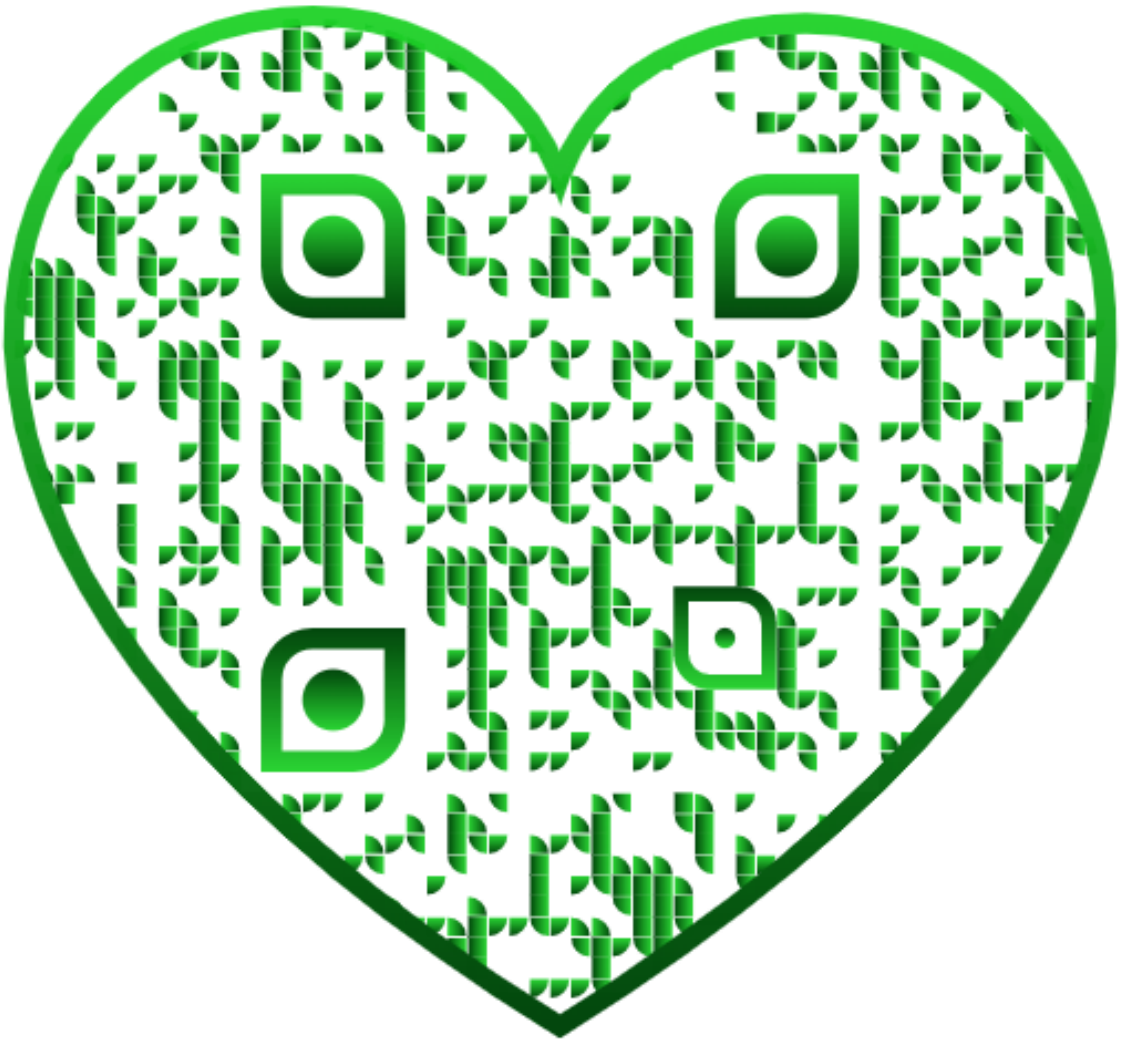
Certain groups are at higher risk for clotting:

- Older people
- People who are obese or overweight
- People with cancer or other conditions (including autoimmune disorders such as lupus)
- People whose blood is thicker than normal because their bone marrow produces too many blood cells

Genetic causes of excessive blood clotting are also important. This happens when there are changes in the genetic code of some proteins needed for clotting, or proteins that work to dissolve blood clots in the body.

Venous thromboembolism is most common in adults 60 and older, but it can occur at any age. VTE is rare in children, though.

Risk Factors:



- Major general surgery
- Major orthopedic surgery
- Lower-extremity paralysis due to spinal cord injury
- Fracture of the pelvis, hip or long bones
- Multiple trauma
- Cancer — all cancers increase the risk, especially if the cancer has spread widely, and if it is cancer of the lung, brain, lymphoma, gynecologic system (like ovary or uterus), or gastrointestinal tract (like pancreas or stomach). In patients with cancer, chemotherapy and surgery for cancer further increase the risk.

Clinical features:

Deep Vein Thrombosis (DVT)

- Pain or tenderness, often starting in the calf
- Swelling, including the ankle or foot
- Redness or noticeable discoloration
- Warmth

Pulmonary Embolism (PE)

- Unexplained shortness of breath
- Rapid breathing
- Chest pain (may be worse upon deep breath)
- Rapid heart rate
- Light headedness or passing out

Pathogenesis:

Venous thromboembolism is associated with **Virchow's triad**: three conditions that predispose to thrombus formation.

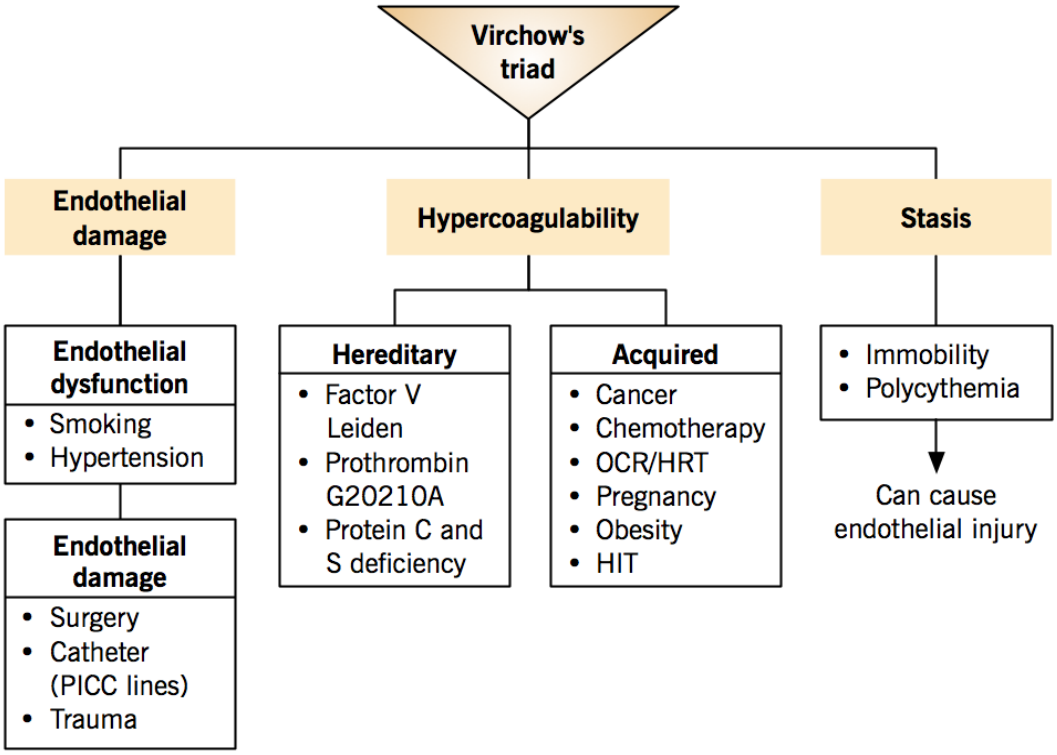
1. Hypercoagulability
2. Stasis
3. Endothelial damage

DVT:

- **Venous valves** are avascular, which, in conjunction with reduced flow of oxygenated blood in veins, predisposes the endothelium to be **hypoxemic**.
- The endothelium around valves responds by expressing adhesion molecules that attract leukocytes. These cells transfer **tissue factor** to the endothelium, which can complex with **activated factor VII** to begin the coagulation cascade via the extrinsic pathway.

PE:

- Platelets from the thrombus secrete chemical mediators such as histamine and serotonin, which causes **pulmonary vasoconstriction** and **bronchoconstriction.**
- Bronchoconstriction leads to **alveolar hypoxemia**, which in turn causes more vasoconstriction and increased vascular resistance.



Diagnosis:

- Diagnosis starts with **history (risk factors) and physical**, which can be used to generate a pretest probability using a validated **clinical prediction rule**, such as the **Wells DVT score**.
- Patients with high likelihood of DVT can be further tested with **compression ultrasonography**, where the length of the proximal veins (popliteal and femoral) is sequentially compressed with the ultrasound probe.
- A **D-dimer** level can be done to rule-out DVT in individuals with low pretest probability (see discussion in Diagnosis of PE).
- **Contrast venography** is considered the gold standard for diagnosis of DVT, although this is rarely done because it is invasive, expensive, and not readily available. Contrast is injected into the dorsal foot vein, and the leg is imaged with CT scan or MRI.

	Criteria	Points
1	Clinical signs/symptoms of DVT	3
2	No other diagnosis more likely than PE	3
3	**Tachycardia**: heart rate > 100	1.5
4	**Immobilization** for > 3 days (e.g. strict bed rest) OR **Surgery** in the previous 4 weeks	1.5
5	Previous DVT or PE	1.5
6	Hemoptysis	1
7	Malignancy	1
	Low risk (<2): **3%** pretest probability Moderate (2-6): **20%** High (>6): **63%** **Thromb Haemost. 2000 M**	

Management:

- To prevent thrombus extension, decrease of the risk of recurrent thrombosis and subsequent death in patient with VTE pharmacological and/or mechanical approaches can be administered
- The goals of treatment for VTE are (i) **anticoagulation** to prevent further clot generation and (ii) **thrombolysis** if the thrombus is large enough to cause hemodynamic compromise.

Anticoagulation: Reduces further clot formation:

Anticoagulation with **parenteral** (intravenous or subcutaneous) and **oral** anticoagulants is the mainstay of VTE therapy. Typically, one of the parenteral agents (e.g. heparin, LMWH, or fondaparinux) or a new oral anticoagulant (e.g. rivaroxaban) is started first. The patient may be transitioned to a traditional oral anticoagulant (e.g. warfarin) for chronic anticoagulation.

- **Unfractionated heparin (UFH)**: Inhibits the function of thrombin as well as Xa by inducing conformational changes in **antithrombin**, allowing it to bind the enzymes better.
- **Low molecular weight heparin (LMWH)**: Functions similar to UFH, but due to the smaller average heparin chain length, accelerates the bridging of AT with Xa only, and not thrombin.

- **Fondaparinux**: A pentasaccharide sequence that directly binds to AT (at an allosteric site) and induces a conformational change allowing it to bind and inhibit factor Xa only.
- **Rivaroxaban:** A new oral anticoagulant that inhibits factor Xa by binding to its active site.

Chronic anticoagulation: For prophylaxis against future VTE:

Any of the agents for acute anticoagulation can be used for chronic anticoagulation, but they are less convenient for outpatients due to the need for daily injections. **Oral anticoagulation drugs** are the mainstay for outpatient anticoagulation. **Vitamin K antagonists (e.g. warfarin)** were traditionally used, but newer agents, such as **dabigatran** and **rivaroxaban**, can also be used. In addition, **aspirin** is an antiplatelet agent that has been shown to reduce VTE events.

- **Vitamin K antagonists (e.g. warfarin)**: Warfarin inhibits the vitamin K dependent synthesis of calcium dependent clotting factors (II, VII, IX and X). Furthermore, warfarin also inhibits PS and PC (part of the endogenous anticoagulation pathway).
- **Direct thrombin inhibitors (e.g. dabigatran):** Directly block thrombin function by blocking the active site. Dabigatran is equivalent to warfarin in both prevention of recurrent clots and bleeding risk in patients with acute VTE.
- **Direct Xa inhibitors (e.g. rivaroxaban):** Directly inhibit the function of Xa by blocking the active site.
- **Aspirin:** Although this antiplatelet agent is classically used to prevent **arterial thrombosis**, new evidence suggests that it can also be used for recurrent VTE prevention. Daily aspirin (100mg/day used in trials) can reduce VTE recurrence by approximately 1/3.

Thrombolysis: Breaks down the thrombus:

- **Tissue plasminogen activator (tPA):** activates plasminogen (Pg) to plasmin (Pn), which cleaves the thrombus, generating soluble D-dimer products.

Contraindications to anticoagulation:

- **Thrombectomy:** If a large thrombus creates hemodynamic compromise, and there are contraindications to thrombolysis, the clot can be **surgically removed** or by interventional radiology.
- **Inferior vena cava (IVC) filter:** Temporary IVC filters can be placed to stop the movement of clots from the deep veins of the lower extremity from travelling to the pulmonary vasculature.